

## INTERNATIONAL SEARCH REPORT

PCT/GB2004/003904

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, EMBASE, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>ENSS M -L ET AL: "Proinflammatory cytokines trigger MUC gene expression and mucin release in the intestinal cancer cell line LS180"  <b>INFLAMMATION RESEARCH,</b>          vol. 49, no. 4, April 2000 (2000-04),          pages 162-169, XP008043079          ISSN: 1023-3830          the whole document</p> <p>-----</p> <p style="text-align: center;">-/-</p>	1-29

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## \* Special categories of cited documents :

- 'A' document defining the general state of the art which is not considered to be of particular relevance
- 'E' earlier document but published on or after the International filing date
- 'L' document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- 'O' document referring to an oral disclosure, use, exhibition or other means
- 'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&amp;' document member of the same patent family

Date of the actual completion of the International search

26 May 2005

Date of mailing of the International search report

10/06/2005

Name and mailing address of the ISA

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## INTERNATIONAL SEARCH REPORT

PCT/GB2004/003904

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>SKEBERDIS VYTENIS A ET AL: "Insulin promotes rapid delivery of N-methyl-D-aspartate receptors to the cell surface by exocytosis"</p> <p>PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 98, no. 6, 13 March 2001 (2001-03-13), pages 3561-3566, XP008043078</p> <p>ISSN: 0027-8424</p> <p>abstract</p> <p>page 3562, right-hand column, line 1 -</p> <p>page 3563, left-hand column, last line</p> <p>-----</p>	1-29
X	<p>JAYAWICKREME S P ET AL: "Regulation of 15-lipoxygenase expression and mucus secretion by IL-4 in human bronchial epithelial cells"</p> <p>AMERICAN JOURNAL OF PHYSIOLOGY - LUNG CELLULAR AND MOLECULAR PHYSIOLOGY 1999 UNITED STATES, vol. 276, no. 4 20-4, 1999, pages L596-L603, XP008043082</p> <p>ISSN: 1040-0605</p> <p>page L600, right-hand column, last paragraph - page L601, right-hand column, line 2</p> <p>-----</p>	1-29
X	<p>ENSS M -L ET AL: "Proinflammatory cytokines differentially affect mucin expression in LS180 cells"</p> <p>GASTROENTEROLOGY, vol. 114, no. 4 PART 2, 15 April 1998 (1998-04-15), page A973, XP008043029</p> <p>&amp; DIGESTIVE DISEASES WEEK AND THE 99TH ANNUAL MEETING OF THE AMERICAN GASTROENTEROLOGICAL ASSOCIATION; NEW ORLEANS, LOUISIANA, USA; MAY 16-22, 1998</p> <p>ISSN: 0016-5085</p> <p>abstract no. G3987</p> <p>the whole document</p> <p>-----</p> <p>-/-</p>	1-29

## INTERNATIONAL SEARCH REPORT

PCT/GB2004/003904

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ABDULLA P ET AL: "GTP and Ca-2+ - dependent mucin secretion in permeabilized LS180 human colonic cancer cells: Modulation by anion substitution" FASEB JOURNAL, vol. 11, no. 3, 1997, page A516, XP008043069 & ANNUAL MEETING OF THE PROFESSIONAL RESEARCH SCIENTISTS ON EXPERIMENTAL BIOLOGY 97; NEW ORLEANS, LOUISIANA, USA; APRIL 6-9, 1997 ISSN: 0892-6638 abstract no. 2989 the whole document -----	1-29
X	DEBINSKI W ET AL: "A NOVEL CHIMERIC PROTEIN COMPOSED OF INTERLEUKIN-13 AND PSEUDOMONAS EXOTOXIN IS HIGHLY CYTOTOXIC TO HUMAN CARCINOMA CELLS EXPRESSING RECEPTORS FOR INTERLEUKIN-13 AND INTERLEUKIN-4" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 270, no. 28, 14 July 1995 (1995-07-14), pages 16775-16780, XP002011861 ISSN: 0021-9258 the whole document -----	1-13, 28, 29
X	WO 98/07864 A (MICROBIOLOGICAL RESEARCH AUTHORITY CAMR (CENTRE FO; THE SPEYWOOD LABOR) 26 February 1998 (1998-02-26) examples -----	1-13, 28, 29
X	WO 94/21300 A (THE SPEYWOOD LABORATORY LTD; PUBLIC HEALTH LABORATORY SERVICE BOARD; N) 29 September 1994 (1994-09-29) claim 14 -----	1-13, 28, 29
X	EP 0 467 536 A (MERCK & CO. INC; MERCK & CO., INC) 22 January 1992 (1992-01-22) examples -----	1-13, 28, 29
X	LI DAILIN ET AL: "Hyperosmolarity reduces GLUT4 endocytosis and increases its exocytosis from a VAMP2-independent pool in L6 muscle cells" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 276, no. 25, 22 June 2001 (2001-06-22), pages 22883-22891, XP002329525 ISSN: 0021-9258 page 22883, right-hand column figures 1,2,10 -----	14-29

## INTERNATIONAL SEARCH REPORT

PCT/GB2004/003904

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>OLSON ANN LOUISE ET AL: "Insulin-mediated GLUT4 translocation is dependent on the microtubule network"  <i>JOURNAL OF BIOLOGICAL CHEMISTRY</i>, vol. 276, no. 14, 6 April 2001 (2001-04-06), pages 10706-10714, XP002329526  ISSN: 0021-9258  page 10706, right-hand column, paragraph 2 - paragraph 3  page 10712, right-hand column, paragraph DISCUSSION</p> <p>-----</p> <p>YANG CHUN ZHI ET AL: "ADP-ribosylation factor 6 (ARF6) defines two insulin-regulated secretory pathways in adipocytes"  <i>JOURNAL OF BIOLOGICAL CHEMISTRY</i>, vol. 274, no. 36, 3 September 1999 (1999-09-03), pages 25297-25300, XP002329527  ISSN: 0021-9258  abstract  page 25297, right-hand column, paragraph 2</p> <p>-----</p> <p>CAIN C C ET AL: "MEMBERS OF THE VAMP FAMILY OF SYNAPTIC VESICLE PROTEINS ARE COMPONENTS OF GLUCOSE TRANSPORTER-CONTAINING VESICLES FROM RAT ADIPOCYTES"  <i>JOURNAL OF BIOLOGICAL CHEMISTRY</i>, vol. 267, no. 17, 1992, pages 11681-11684, XP002329528  ISSN: 0021-9258  abstract  page 11684, left-hand column, paragraph CONCLUSIONS - right-hand column</p> <p>-----</p> <p>DAVIS R J ET AL: "INSULIN-LIKE GROWTH FACTOR I AND EPIDERMAL GROWTH FACTOR REGULATE THE EXPRESSION OF TRANSFERRIN RECEPTORS AT THE CELL SURFACE BY DISTINCT MECHANISMS"  <i>JOURNAL OF BIOLOGICAL CHEMISTRY</i>, vol. 262, no. 27, 1987, pages 13126-13134, XP002329529  ISSN: 0021-9258  abstract  page 13128, left-hand column, line 6 - right-hand column, line 2  figures 1-4</p> <p>-----</p>	14-29
X		14-29
X		14-29
X		14-29

**INTERNATIONAL SEARCH REPORT**

PCT/GB2004/003904

**Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.: 1-13, 28 and 29 in part because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
  
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

1-29

4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 28-29 in part, and 1-13

Method of designing a non-cytotoxic toxin as defined by these claims  
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2. claims: 28-29 in part, and 14-27

Method of identifying an agonist as defined in these claims.  
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3. claims: 30-43 and 48-57 in part

Pharmaceutical composition and its use (in a method of treatment) as defined in these claims, in which the TM of the agent is IL-13  
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4. claims: 30-43 and 48-57 in part

Pharmaceutical composition and its use (in a method of treatment) as defined in these claims, in which the TM of the agent is insulin  
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5. claims: 30-43 and 48-57 in part

Pharmaceutical composition and its use (in a method of treatment) as defined in these claims, in which the TM of the agent is mast cell degranulating peptide.  
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6. claims: 30-43 and 48-57 in part

Pharmaceutical composition and its use (in a method of treatment) as defined in these claims, in which the TM of the agent is IL-4  
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7. claims: 30-43 and 48-57 in part

Pharmaceutical composition and its use (in a method of treatment) as defined in these claims, in which the TM of the agent is TNF alpha  
---

8. claims: 30-43 and 48-57 in part

Pharmaceutical composition and its use (in a method of treatment) as defined in these claims, in which the TM of the agent is EGF.  
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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

9. claims: 44-45

DNA construct as defined in claim 44, and its use in the preparation of a chimeric agent as defined in claim 45

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10. claims: 46-47

Process of preparing a conjugate as defined in these claims, i.e., by conjugation rather than by expression of a single DNA construct.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1-13, 28 and 29 in part

Claims 1-13, 28 and 29 encompass a genus of compounds defined only by their function wherein the relationship between the structural features of the members of the genus and said function have not been defined. In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition. The fact that one could have assayed a compound of interest using the claimed assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity. Therefore, the search for claims 1-13, 28 and 29 has been limited to the examples (Art. 5 and Art. 6 PCT), insofar as relating to the first invention.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

## INTERNATIONAL SEARCH REPORT

PCT/GB2004/003904

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 9807864	A	26-02-1998	AT AU AU CA EP WO JP US US ZA	294238 T 723397 B2 4389597 A 2264191 A1 0939818 A1 9807864 A1 2001502890 T 2003166238 A1 2002044950 A1 9707541 A	15-05-2005 24-08-2000 06-03-1998 26-02-1998 08-09-1999 26-02-1998 06-03-2001 04-09-2003 18-04-2002 16-04-1998
WO 9421300	A	29-09-1994	AT AU AU BR CA CN CZ DE DE DK EP ES FI WO HU IN JP NO NZ PL PT SG SK	228856 T 671203 B2 6217594 A 9406232 A 2158647 A1 1124929 A 9502426 A3 69431832 D1 69431832 T2 689459 T3 0689459 A1 2183836 T3 954390 A 9421300 A2 76556 A2 178499 A1 9500867 T 953643 A 262484 A 310698 A1 689459 T 73411 A1 115595 A3	15-12-2002 15-08-1996 11-10-1994 09-01-1996 29-09-1994 19-06-1996 17-04-1996 16-01-2003 10-04-2003 24-03-2003 03-01-1996 01-04-2003 17-11-1995 29-09-1994 29-09-1997 03-05-1997 28-01-1997 16-11-1995 27-08-1996 27-12-1995 30-04-2003 20-06-2000 05-02-1997
EP 0467536	A	22-01-1992	AT AU AU CA DE DE DK EP EP ES FI IE JP JP JP NO PT US ZA	173274 T 645094 B2 7918991 A 2044858 A1 69130466 D1 69130466 T2 467536 T3 0467536 A2 0868920 A2 2122968 T3 913058 A 912130 A1 1988090 C 5092999 A 7021000 B 912418 A 98048 A ,B 5690928 A 9104757 A	15-11-1998 06-01-1994 02-01-1992 22-12-1991 17-12-1998 02-06-1999 26-07-1999 22-01-1992 07-10-1998 01-01-1999 22-12-1991 01-01-1992 08-11-1995 16-04-1993 08-03-1995 23-12-1991 30-04-1992 25-11-1997 25-03-1992